IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Applicant: Naidu, Satyanarayan A.

For: IMMOBILIZED LACTOFERRIN (*Im*-LF) ANTIMICROBIAL AGENTS AND USES THEREOF

(US-PCT-106099)

Examiner: Russel, Jeffrey E.
Group Art Unit: 1654

APPEAL BRIEF
Appeal of Final Office Action of April 7,2005

CERTIFICATE OF MAILING (37 CFR 1.8(A))
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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Sir:

Enclosed is a Petition for a two month Extension of Time and a check for the requisite fee, so that the period for submitting this brief now runs to and includes November 7, 2005.

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(1) Real Parties in Interest

A. Satyanarayan Naidu, an individual living at 9200 Monte Vista Ave., No. 3, Montclair, CA 91763, LF Tech, a limited liability company having an office at 299 S. Main Street, Suite 2450, Salt Lake City, UT 84111, and aLF Ventures, a limited liability company having an office at 299 S. Main Street, Suite 2450, Salt Lake City, UT 84111 are the real parties in interest.

(2) Related Appeals and Interferences

Neither Appellant, Appellant's legal representative, or his assignees are aware of any other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

Currently pending are claims 1-49, 51, and 56-202. Claims 6-10, 14-17, 40-49, 51, 59-61, 63, 66, 67, 69-85, 91, 93-100 and 118 have been allowed. Claims 3, 4, 12, 13, 21, 23-27, 29, 30, 33-37, 56-58, 62, 64, 65, 68, 87-90, 92, 105, 107-114, 125, 130, 139-141, 152, 155, 156, 160, 161, 166-170, 174, 177, 178, 182, 183, 188-192, 198, and 199 have been objected to. Claims 1, 2, 5, 11, 18-20, 22, 28, 31, 32, 38, 39, 86, 101-104, 106, 115-117, 119-124, 126-129, 131-138, 142-151, 153, 154, 157-159, 162-165, 171-173, 175, 176, 179-181, 184-187, 193-197, and 200-202 have been rejected.

(4) Status of Amendments

The Examiner mailed a Final Office Action on April 7, 2005. The Applicant filed a proposed amendment on August 26, 2005. In an Advisory Action mailed September 13, 2005, the Examiner notified the Applicant that for the purposes of this appeal, the proposed amendments would not be entered.

(5) **Summary of Invention**

This application relates to antimicrobial agents and their use. (Specification, page 1, line 10.) Lactoferrin (LF) is a known antimicrobial agent. (Specification, page 8, lines 10 and 11.) LF is a glycol-protein having a bilboate structure, with an N-terminus lobe and a C-terminus lobe. (Specification, page 8, lines 15 and 16.) The activity of LF is highly dependent on its three-dimensional or tertiary structure. (Specification, page 8, lines 23 and 24.) If the protein dos not have the proper conformation, its activity is diminished or lost. (Specification, page 8, lines 24 and 25.) LF can be immobilized by mixing the LF with the naturally occurring substrate in a suitable medium, such as deionized water. (Specification, page 13, lines 5-7.)

Claims 38 and 39 are directed to specific concentrations of immobilized lactoferrin on the surface of the composition subject to microbial contamination. Claims 149-151, 153, 164, 171-173, 175, 186, 193-195, and 197 are directed to a method for reducing the microbial contamination of a human or non-human vertebrate subject to microbial contamination using immobilized LF.

(6) **Issues**

(i) Whether claims 102-104, 115-117, 119, 124, 127, 128, 137, 138, 142-148, 154, 157, 158, 171, 172, 176, 179, 180, 186, and 193-196 are unpatentable under 35 U.S.C. §102(e) as being anticipated by US 6,475,511 B2 ("Gohlke *et al.*").

(ii) Whether claims 1, 11, 19, 28, 31, 39, 101-102, 119-124, 126-129, 131, 132, 134, 142-148, 197, and 200 are unpatentable under 35 USC §102(b) as being anticipated by WO Patent Application 91/13982 ("WO Patent Application '982").

(iii) Whether claims 149-151, 153, 164, 171-173, 175, 186, and 193-195 are unpatentable under 35 USC §103(a) as being obvious in view of WO Patent Application 91/13982 ("WO Patent Application '982").

(iv) Whether claims 1, 2, 5, 18, 19, 22, 31, 101-103, 106, 115-117, 119-124, 126-129, 131-132, 134, 136, 142-151, 153, 164, 171-173, 175, 186, 193-197, and 200-202 are unpatentable under 35 USC § 102(b) as being anticipated by European Patent Application 753,309 ("European Patent Application '309").

(v) Whether claims 38 and 39 are unpatentable under 35 USC §103(a) as being obvious in view of European Patent Application 753,309 ("European Patent Application '309").

(vi) Whether claims 1, 2, 5, 18, 19, 22, 31, 32, 101-103, 106, 115, 119-124, 126-129, 131-136, 142-151, 153, 159, 162-165, 171-173, 175, 181, 184-187, 193-197, and 200-202 are unpatentable under 35 USC §102(b) as being anticipated by European Patent Application 753,308 ("European Patent Application '308").

(vii) Whether claims 38 and 39 are unpatentable under 35 USC §103(a) as being obvious in view of European Patent Application 753,308 ("European Patent Application '308").

(viii) Whether claims 1-3, 5, 18-20, 22, 31, 32, 102-104, 106, 115, 119, 124, 137, 138, 142-150, 154, 164, and 165 are unpatentable under 35 USC §102(e) as being anticipated by US Patent 6,066,469 by Kruzel *et al.* ("Kruzel *et al.*").

(7) **Grouping of the Claims**

For the purpose of this appeal, the claims within each of the following groups will stand or fall together.

Group 1: 1, 2, 5, 18, 19, 22, 31, 38, 39, 104, 106, 120, 121, 122, 123, , 129, 131, 132, 134, 136, 149, 150, 151, 153, 162, 163, 164, 165, 173, 175, 186, 197, 200, 201, and 202.

Group 2: 102, 103, 115, 116, 117, 119, 127, 128, 142, 143, 144, 145, 146, 147, 148, 171, 172, 193, 194, 195, and 196.

Group 3: 104, 137, 138, 154, 157, 158, 176, 179, and 180.

Group 4: 133, 135, 159, 181, 184, 185, and 187.

Group 5: 11 and 28.

Group 6: 20.

(8) **Argument**

I. Summary of Argument

The appealed claims all require, *inter alia*, the immobilization of lactoferrin on a naturally occurring substrate via the lactoferrin's N-terminus region. The examiner relies on a number of references which are alleged to inherently disclose such immobilized lactoferrin. However, the examiner provides no evidence that such immobilization occurs and, consequently, has failed to establish the requisite *prima facie* basis for the rejections.

In marked contrast, applicant has provided factual evidence, in the form of the declaration of Dr. Andrew Barron, establishing that none of the references relied on by the examiner inherently discloses the formation of lactoferrin immobilized on a naturally occurring substrate via the lactoferrin's N-terminus region. As explained by Dr. Barron, the reasons that immobilization cannot occur are because (1) the "substrates" are too small to immobilize lactoferrin, (2) the "substrates" do not possess the proper charge to bind lactoferrin's positively charged N-terminus, or (3) the proper conditions for immobilization are not described.

Because one or more of Applicant's arguments apply to each of the rejected claims, Applicant has grouped the claims as shown in Section (7) above. Group 1 consists of the claims that are distinguished over the references cited against them by Applicant's argument numbered 2) above. Group 2 consists of the claims that are distinguished over the references cited against them by Applicant's arguments numbered 1) and 3) above. Group 3 consists of the claims that are distinguished over the references cited against them by Applicant's argument numbered 3) above. Group 4 consists of the claims that are distinguished over the references cited against them by Applicant's arguments numbered 1) or 2) above. Group 5 consists of the claims that are distinguished over the references cited against them by Applicant's arguments numbered 1) or 2) or 3) above. Group 6 consists of the claims that are distinguished over the references cited against them by Applicant's arguments numbered 1) or 3) above.

II. Examiner's Burden

The examiner bears the burden of establishing a *prima facie* basis for each ground for rejection of the claims on appeal. *In re Alton*, 76 F.3d 1168, 1175 (Fed. Cir. 1996); *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992).

With respect to the core factual findings in a determination of a lack of patentability, the examiner cannot simply reach conclusions based on his own understanding or experience or on his assessment of what would be basic knowledge of common sense. *In re Zurko*, 258 F.3d 1379, 1386 (Fed. Cir. 2001.) Instead, the examiner must point to some concrete evidence in the record to support the findings underlying the rejections. (*Id.*) As stated in *Continental Can. Co. USA, Inc. v. Monsanto*, 948 F.2d 1264, 1268 and 1269 (Fed. Cir. 1991):

> "To serve as anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to **extrinsic evidence**. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. In re Oelrich, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981)

(Bold added.)

Continental Can was cited with approval in In re Robertson, 169 F.3d 743, 745 (Fed. Cir. 1999), where the court explained:

> "To establish inherency, the **extrinsic evidence** 'must make clear that the missing descriptive matter is **necessarily present** in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' *Continental Can. Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991). 'Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not

sufficient.' Id. At 1269, 948 F.2d 1264, 20 U.S.P.Q.2d at 1749 (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981))." (Bold added.)

The examiner has failed to provide any such concrete evidence to support his assertions that the references inherently disclose lactoferrin immobilized on a naturally occurring substrate via the lactoferrin's N-terminus region and, therefore, the rejections should be withdrawn.

III. Declaration of Dr. Andrew R. Barron

Applicant submitted the Declaration of Dr. Andrew R. Barron, under 37 C.F.R. §1.132, on August 24, 2004. Dr. Barron received A.R.C.S. and B.Sc. (1st Class, Hones.) degrees, majoring in chemistry, at Imperial College of Science and Technology, University of London in 1986. (Barron Decl., ¶ 1.) He received a D.I.C. and Ph.D., at the same university in 1986. (*Id.*) He was a Post-Doctoral Research Associate, at the University of Texas, Austin in 1986-1987. (*Id.*)

Dr. Barron was an Assistant Professor and then an Associate Professor, at Harvard University from 1987 to 1995. (Barron Decl., ¶ 2.) In the fall of 1995, he went to Rice University, where he is currently the Charles W. Duncan, Jr. - Welch Chair of Chemistry and Professor of Materials Science in the Department of Chemistry and Department of Mechanical Engineering and Materials Science. (Barron Decl., ¶ 3.) He has authored over two hundred journal articles and has made a like number of presentations. (Barron Decl., ¶ 4.)

Lactoferrin (LF) is a protein (or peptide). (Specification, page 11, lines 13 and 14.) A full length LF peptide sequence has about 600 to about 800

continuous amino acids. (Barron Decl., ¶ 7.) Human LF, in particular, is about 703 amino acids long and has a molecular weight of about 83,000 daltons. (*Id.*) Furthermore, as explained by Dr. Barron, LF has a bilboate structure, with a positively charged N-terminus lobe and a negatively charged C-terminus lobe. (*Id.*)

LF is a known antimicrobial agent. (Specification, col. 8, lines 10 and 11.) Its activity is highly dependent on its three-dimensional or tertiary structure. (Specification, col. 8, lines 23 and 24.) If LF does not have the proper conformation, its activity is diminished or lost. Specification, col. 8, lines 24 and 25.)

Now it has been unexpectedly found that LF can be stabilized and its antimicrobial activity increased, if the LF is immobilized by binding its N-terminus to a suitable, naturally occurring substrate, *i.e.,* if LF has its N-terminus region attached to a substrate leaving the C-terminus region free to interact with microbes. (Appl. page 7, line 34-page 8, line 3.) Consequently, among the requirements for LF to become immobilized on a substrate and, in particular on a naturally occurring substrate, the portion of the substrate which is to do the binding should carry the opposite charge, *i.e.*, carry a negative charge. (Barron Decl., ¶ 9.)

The examiner discounts Dr. Barron's declaration. The examiner asserts that the declaration should be ignored, because Dr. Barron "performs no direct testing on the prior art compositions in order to determine whether or not they comprise LF immobilized on a naturally occurring substrate via the N-terminus region of the LF," but "attempt[s] to show by scientific reasoning and/or argument that the prior art compositions [sic] do not teach this feature."

Applicant disagrees with the examiner's refusal to consider Dr. Barron's declaration. Dr. Barron's declaration must be considered and it is persuasive on the issue of whether any of the references relied upon by the examiner inherently disclose LF immobilized on a naturally occurring substrate via the N-terminus region of the LF. Dr. Barron's declaration has a well founded factual basis that is entirely consistent with the disclosure set forth in applicant's specification. There is no requirement that a declaration submitted under 37 C.F.R. 1.132 must be based on direct testing. For example, in *In re Alton*, 76 F.3d at 1175, the Federal Circuit held that the examiner had erred in dismissing a declaration based on "statements of fact."

The examiner further asserts that:

> "One major argument made by Declarant and in the Remarks is that '[f]or the N-terminus region to become immobilized on a naturally occurring substrate, the region of the substrate to which the N-terminus region is to become attached should carry the opposite charge, i.e., carry a negative charge. . .' However, Declarant does not provide any citation to the specification which would support this contention, and the examiner can find no support in the original disclosure of the invention for this contention."

Support for the contention is provided by applicant's frequent and unequivocal teaching that LF must be immobilized on the substrate via the N-terminus region of the LF. Applicant was not required to provide an explanation in the specification concerning how his invention worked, *i.e.*, how the N-terminus region is immobilized on the substrate. *Newman v. Quigg*, 877 F.2d 1575, 1581 (Fed. Cir. 1989). Dr. Barron's explanation – that to be immobilized, the positive N-terminus region must bind with a negatively

charged substrate – is of importance only in the context of subsequently trying to help the examiner understand how the invention is distinguishable over the prior art.

The examiner additionally argues that:

> "Further, this argument is inconsistent with the disclosure in the specification of useful substrates which do not have a positive charge. For example, the original specification at page 10, line 22, and originally-filed claim 3 disclose triglycerides to be useful substrates for immobilizing lactoferrin by its N-terminus region. Triglycerides are uncharged. The original specification at page 10, lines 19-22, and originally-flied claim 3 disclose proteins, polysaccharides, and lipids to be useful substrates for immobilizing lactoferrin by its N-terminus. These classes of compounds embrace positively charged, negatively charged, and uncharged compounds."

However, what is clear when the application is considered in its entirety is that a suitable substrate must be one on which the LF becomes immobilized via its N-terminus. For example, originally filed dependent claim 3 did not simply, cover specific substrates. Instead, the substrates were subject to the limitation that the LF must be immobilized via its N-terminal region. For the reasons given by Dr. Barron, LF cannot bind to triglycerides and other lipids via its N-terminal region. (It is important to note that there is nothing in the record that contradicts Dr. Barron's declaration. None of the references relied upon by the examiner suggest that LF can become immobilized on lipids, such as triglycerides.) Consequently, what is inconsistent with applicant's overall teachings is applicant's initial recitation of triglycerides and other lipids – not Dr. Barron's declaration.

Similarly, applicant has never stated that all proteins and polysaccharides are useful. They too are subject to the limitation that the LF must be immobilized on the substrate via its N-terminal region. There are numerous examples of suitable proteins and polysaccharides. Useful proteins include fibronectin, casein and mucin, while suitable polysaccharides include galactose-rich polysaccharides, collagen, heparin-sulfate, and carrageenan. (Page 10, lines 19-23.) These all contain negatively charged regions and, accordingly, are all consistent with Dr. Barron's explanation of what it takes to immobilize LF by its N-terminus region. Therefore, Dr. Barron's declaration is not inconsistent with the claimed invention.

Still further, the examiner asserts:

> "Finally, this argument by Declarant uses a significant qualifier "should." Because of this use of this word, Declarant in effect admits that a substrate does not have to have a negative charge in order to be useful in immobilizing lactoferrin by its N-terminus."

Applicant respectfully disagrees. The primary definition of "should" as found in Merriam-Webster's Collegiate Dictionary, Eleventh Addition, p. 1153 is "**1** -- used in auxiliary function to express condition <if he ~ leave his father, his father would die – Gen 44:22<RSV>" Dr. Barron uses "should" in this same conditional sense – if LF is to be bound to the substrate via its N-terminus, the substrate ~ have a region carrying a negative charge. Therefore, Dr. Barron's use of the word "should," supports the argument that LF must be immobilized on a substrate having a negative region.

IV. Gohlke *et al.* does not Anticipate the Claimed Invention

US 6,475,511 B2 ("Gohlke *et al.*") do not anticipate any of claims 102-104, 115-117, 119, 124, 127, 128, 137, 138, 142-148, 154, 157, 158, 171, 172, 176, 179, 180, 186, and 193-196 under 35 U.S.C. §102(e). Gohlke *et al.* describe compositions containing a combination of colostrum and LF in a "mucosal delivery format" ("MDF"). (Col. 6, lines 13-28.) The composition can also contain modified pectin. (Col. 6, lines 49-52.) By MDF is meant a composition, such as a lozenge, formed of *solid* components. (Barron Decl., ¶ 11.) For example, Gohlke *et al.* teach, "The individual components of the composition may be obtained from commercial sources: colostrum (which is dehydrated by standard spray-drying procedures known in the art)" (col. 9, lines 41-44). Furthermore, examples 1 - 3 describe a process for preparing the compositions where, "[E]ach of the following ingredients is placed, in *powdered* form, into a commercial mixer." (Emphasis added.) The ingredients are then mixed and *cold pressed.*

A. Gohlke *et al.* does not Teach the Formation of Immobilized LF

The examiner argues that:

> "With respect to Gohlke *et al* (U.S. Patent No. 6,475,511), Declarant argues that cold pressing as occurs in Gohlke *et al* will not provide an environment suitable to cause lactoferrin to become attached to the colostrum or the modified pectin via the lactoferrin's N-terminus region. However, Declarant does not provide any reasoning or evidence as to why these processing steps of Gohlke *et al* are insufficient to result in immobilization via the N-terminus of lactoferrin.
>
> "Further, there is no disclosure anywhere in the specification that *special procedures or conditions* are necessary in order to achieve the

desired immobilization. See, e.g., page 11, lines 3-11, of the specification. In the absence of a disclosed need for special conditions, Gohlke *et al's* disclosed thorough mixing and cold pressing of the ingredient in powder form is deemed to be sufficient to result in the claimed immobilization."
(Emphasis added.)

However, Dr. Barron makes plain that immobilized LF will not be formed, if LF is simply admixed with another solid. He explains, "The mere presence of LF in a cold-pressed mixture with other *solids*, such as colostrum and modified pectin in an MDF format, would not inherently result in the LF becoming attached via its N-terminus." (Barron Decl., ¶ 13, emphasis added.)

Furthermore, it is not clear what the examiner means by "special conditions." Applicant teaches that LF is immobilized on the substrate using a *suitable* technique and gives as an example "mixing the LF with the biologically active substrate in a suitable medium, such as deionized water." (Specification, page 11, lines 3-5.) Accordingly, nothing in the specification, in Gohlke *et al.* or in any of the other references contradicts Dr. Barron's declaration and suggests that LF can become immobilized simply by admixing with another solid. Therefore, Gohlke *et al.* does not anticipate any of claims 102-104, 115-117, 119, 124, 127, 128, 137, 138, 142-148, 154, 157, 158, 171, 172, 176, 179, 180, 186, and 193-196, so that this ground for rejection should be withdrawn.

V. WO Patent Application '982 does not Anticipate the Claimed Invention

WO Patent Application 91/13982 ("WO Patent Application '982") does not anticipate any of claims 1, 2, 11, 18, 19, 28, 31, 39, 101-103, 119-124, 126-

129, 131, 132, 134, 142-148, 197, and 200 under 35 USC §102(b) as being anticipated by WO Patent Application '982. WO Patent Application '982 generally relates to human LF expressed using recombinant DNA. It discloses the use of this LF as a nutritional supplement, an antiseptic, and as a food-spoilage retardant. The LF can be compounded with certain carriers or diluents.

WO Patent Application '982 neither broadly teaches LF immobilized on a naturally occurring substrate via the N-terminus region of the LF, nor does it provide a specific example of such an immobilized LF. (Barron Decl., ¶ 15.) The examiner suggests that:

"The WO Patent Application '982 teaches LF in combination with stearic acid (which is a lipid and also corresponds to Applicant's pharmaceutically acceptable carrier of claim 102) or its salts . . . Because the same components are present in the same defined dispersion, inherently the LF in the composition of the WO Patent Application '982 will be immobilized via its N-terminus. . ."

A. WO Patent Application '982 does not Teach the Formation of Immobilized LF

The *mere presence* in a mixture of LF and stearic acid would *not* form LF immobilized on LF via its N-terminus. WO Patent Application '982 does not disclose or suggest any conditions under which the compounds could be mixed to achieve such immobilization. Merely compounding solid LF with solid stearic acid, such as by cold-pressing the solid ingredients, will not provide an environment suitable to cause the LF to become immobilized via its N-terminus region. Instead, appropriate conditions must be chosen before immobilization can occur. As described in the instant application, LF is immobilized by first

mixing the LF with the naturally occurring substrate in *a suitable medium,* such as deionized water.

The examiner asserts that:

> "Declarant also argues that mere compounding will not result in lactoferrin's attachment to the stearic acid through the N-terminus of the lactoferrin. However, Declarant does not provide any reasoning or evidence to support this argument, and there is not disclosure any where (sic) in the specification that *special procedures or conditions* are necessary in order to achieve the desired immobilization. Further, because stearic acid has a negatively charged carboxyl group, all that it would take for the positively charged N-terminus of lactoferrin to become immobilized on the negatively charged carboxyl group would be to bring the two opposite charges into close physical proximity – charge attraction will do the remainder of the work. Any pharmaceutical compounding step will provide the necessary physical proximity so that at least some of the lactoferrin is immobilized by its N-terminus to a (sic) least some of the stearic acid.

(Emphasis added.)

On the contrary, Dr. Barron makes plain that simply compounding LF with stearic acid will not result in LF's attachment. As Dr. Barron explains, "Merely compounding solid LF with other solids, such as stearic acid, will not provide an environment suitable to cause the LF to become attached to the other solid via LF's N-terminus region." (Barron Decl., ¶ 11.) The basis for his reasoning is readily apparent, merely admixing two solids, even if they have regions of opposing charges, does not provide the conditions necessary for immobilization to occur.

Furthermore, it is not clear what is meant by "special procedures or conditions". Applicant teaches that LF is immobilized on the substrate using a *suitable* technique and gives as an example "mixing the LF with the biologically active substrate in a suitable medium, such as deionized water." (Specification, page 11, lines 3-5.) Accordingly, nothing in the specification, in WO Patent Application '982 or any of the other references relied upon by the examiner contradicts Dr. Barron's declaration and suggests that LF can become immobilized by using "any pharmaceutical compounding step."

B. WO Patent Application '982 does not Disclose any Compounds having the Size Required of a Substrate in order to Immobilize LF

Moreover, stearic acid, with a molecular weight of only 284.47, is too small to be used as a naturally occurring substrate as the term is to be understood in the context of the instant specification and claims. That would be akin to saying that a dog was immobilized on a flea, if a flea attached itself to a dog.

The examiner asserts that:

"This argument cannot be accepted because it contradicts the original disclosure of substrates with molecular weights significantly less than that of lactoferrin. For example, page 10, lines 19-22, of the specification and originally-filed claim 3 recite that nucleic acids, nucleotides, lipids, adenosine triphosphate, and triglycerides are useful and acceptable substrates. These exemplified substrates have molecular weights which are significantly less than that of lactoferrin. Accordingly,

stearic acid can not be disqualified as a substrate merely because of its molecular weight."

What is wrong, however, is not applicant's argument, as supported by Dr. Barron's declaration. Instead, what was wrong was the original inclusion of lipids, such as stearic acid, among the examples of suitable substrates. The reality is that LF cannot be immobilized by a lipid. As explained by Dr. Barron, "Stearic acid with a molecular weight of only 284.47 is not a substrate. LF could not become immobilized on such a small molecule." (Barron Decl., ¶ 17.) Therefore, the rejection of claims 1, 2, 11, 18, 19, 28, 31, 39, 101-103, 119-124, 126-129, 131, 132, 134, 142-148, 197, and 200 as obvious in view of WO Patent Application '982 should be withdrawn.

VI. WO Patent Application '982 Would not have Made Obvious the Claimed Invention

WO Patent Application 91/13982 ("WO Patent Application '982") would not have made obvious claims 149-151, 153, 164, 171-173, 175, 186, 193-195, and 197, the claims covering a method for reducing the microbial contamination of a human or non-human vertebrate subject to microbial contamination. The examiner argues that:

"The WO Patent Application '982 teaches administering its antiseptics to mammals, but does not particularly teach treating humans or non-human vertebrates. It would have been obvious to one of ordinary skill in the art at the time of Applicant's invention was made to use the antiseptic compositions of the WO Patent Application '982 to treat both human and non-human mammals . . ."

However, for the reasons discussed immediately above, WO Patent Application '982 would not have suggested immobilizing LF on a naturally occurring substrate via its N-terminus region. Therefore, the rejection of claims 149-151, 153, 164, 171-173, 175, 186, 193-195, and 197 as being obvious in view of WO Patent Application '982 should be withdrawn.

VII. European Patent Application '309 does not Anticipate the Claimed Invention

European Patent Application 753,309 ("European Patent Application '309") does not anticipate any of claims 1, 2, 5, 18, 19, 22, 31, 101-103, 106, 115-117, 119-124, 126-129, 131-132, 134, 136, 142-151, 153, 164, 171-173, 175, 186, 193-197, and 200-202 under 35 USC § 102(b). European Patent Application '309 generally relates to the preparation of mixtures of LF and desferrioxamine methanesulphonate useful for the therapy of viral infectious diseases.

European Patent Application '309 neither broadly teaches LF immobilized on a naturally occurring substrate via the N-terminus region of the LF, nor does it provides a specific example of such an immobilized LF. (Barron Decl., ¶ 21.) The examiner asserts that:

> "The European Patent Application '309 teaches compositions comprising LF and carriers such as paraffin oil and Vaseline (which are lipids), xantan gum and corn starch (which are polysaccharides), and lecithin (which is an emulsifier) . . . . Because the same components are present in the same defined dispersion, inherently the LF in the composition of the

European Patent Application '309 will be immobilized by its N-terminus . . ."

A. <u>European Patent Application '309 does not Disclose any Compounds having the Size Required to Immobilize LF</u>

Paraffin oil or, as it is alternatively called mineral oil, is a mixture of liquid hydrocarbons. (Concise Chemical and Technical Dictionary, H. Bennett, Ed., Chemical Publishing Co., Inc. (1974) (pp. 702 and 777)) Vaseline is a petroleum jelly, *i.e.*, a purified mixture of semi-solid hydrocarbons. (*Id.*, pp. 798 and 1100.) They are low molecular weight compounds, not substrates, and LF could not become immobilized on such small molecules. (Barron Decl., ¶ 23.)

Similarly, lecithin is a low molecular weight compound. (Barron Decl., ¶ 27.) LF could not become immobilized on such a small molecule. (*Id.*)

B. <u>European Patent Application '309 does not Disclose any Compounds having the Charge Required to Immobilize LF</u>

Additionally, paraffin oil and Vaseline are both hydrocarbons, so that they do not carry any charges. (Barron Decl., ¶ 25.) As a result, neither paraffin oil nor Vaseline contains a region which will attach LF's positively charged N-terminus region. (*Id.*)

Similarly, xanthan gum and corn starch do not carry any charges. (Barron Decl., ¶ 26.) As a result, neither xanthan gum nor corn starch contains a region which will attach LF's positively charged N-terminus region. (*Id.*)

Applicant's arguments are fully supported by Dr. Barron's declaration. Applicant has never asserted that all polysaccharides are useful. On the contrary, the polysaccharides are subject to the limitation that the LF must be immobilized to the substrate via its N-terminal region. Therefore, the claims do not read on low molecular weight compounds, such as paraffin oil, Vaseline, and lecithin or on compounds lacking the negatively charged region needed to immobilize the N-terminus region of LF, such as paraffin oil, Vaseline, xanthan gum or corn starch. Therefore, the rejection of claims 1, 2, 5, 18, 19, 22, 31, 101-103, 106, 115-117, 119-124, 126-129, 131-132, 134, 136, 142-151, 153, 164, 171-173, 175, 186, 193-197, and 200-202 as being anticipated by European Patent Application '309 should be withdrawn.

VIII. European Patent Application '309 Would not have Made Obvious the Claimed Invention

European Patent Application '309 would not have made obvious claims 38 or 39, the claims additionally specifying the concentration of lactoferrin on the surface of the composition subject to microbial contamination, under 35 USC § 103(a).

The examiner argues that:

> "The European Patent Application '309 does not teach a lactoferrin/surface area ratio for surfaces to be treated. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention ws made to determine all operable and optimal does for the lactoferrin-containing compositions . . ."

However, for the reasons discussed immediately above, European Patent Application '309 would not have suggested immobilizing LF on a naturally

occurring substrate via its N-terminus region. Therefore, European Patent Application '309 would not have made obvious either claim 38 or 39, so that this ground for rejection should be withdrawn.

IX. European Patent Application '308 does not Anticipate the Claimed Invention

European Patent Application 753,308 ("European Patent Application '308") does not anticipate any of claims 1, 2, 5, 18, 19, 22, 31, 32, 101-103, 106, 115, 119-124, 126-129, 131-136, 142-151, 153, 159, 162-165, 171-173, 175, 181, 184-187, 193-197, and 200-202 under 35 USC §102(b). European Patent Application '308 generally relates to the use of LF for therapy of diseases caused by Gram positive pathogen microorganisms.

European Patent Application `308 neither broadly teaches LF immobilized on a naturally occurring substrate via the N-terminus region of the LF, nor does it provide a specific example of such an immobilized LF. (Barron Decl., ¶ 26.) The examiner asserts that:

> "The European Patent Application '308 teaches compositions comprising LF and peppermint oil, gum base and corn starch (which are polysaccharides) . . . Because the same components are present in the same defined dispersion, inherently the LF in the composition of the European Patent Application '308 will be immobilized via its N-terminus . . ."

A. European Patent Application '308 does not Disclose any Compounds having the Size Required to Immobilize LF

Peppermint oil is a low molecular weight compound. LF could not become immobilized on such a small molecule. (Barron Decl., ¶ 28.)

B. European Patent Application '308 does not Disclose any Compounds having the Charge Required to Immobilize LF

Furthermore, peppermint oil, gum base and corn starch do not carry any charges. As a result, neither peppermint oil, gum base nor corn starch contain a region which will attach LF's positively charged N-terminus region.

Applicant's arguments are fully supported by Dr. Barron's declaration. Applicant has never asserted that all polysaccharides are useful. On the contrary, the polysaccharides are subject to the limitation that the LF must be immobilized to the substrate via its N-terminal region. Therefore, the claims do not read on low molecular weight compounds, such as peppermint oil or on compounds lacking the negatively charged region needed to immobilize the N-terminus region of LF, such as gum base or corn starch. Nor would such low molecular weight or neutral compounds have suggested a composition of matter comprising LF immobilized on a substrate via the N-terminus region of the LF. Therefore, the rejection of claims 1, 2, 5, 18, 19, 22, 31, 32, 101-103, 106, 115, 119-124, 126-129, 131-136, 142-151, 153, 159, 162-165, 171-173, 175, 181, 184-187, 193-197, and 200-202 as being anticipated by European Patent Application '308 should be withdrawn.

X. European Patent Application '308 Would not have Made Obvious the Claimed Invention

European Patent Application '308 would not have made obvious claims 38 or 39, the claims specifying the concentration of lactoferrin on the surface of the composition subject to microbial contamination, under 35 USC § 103(a).

The examiner argues that:

> "The European Patent Application '308 does not teach a lactoferrin/surface area ratio for surfaces to be treated. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal does for the lactoferrin-containing compositions . . ."

However, for the reasons discussed immediately above, European Patent Application '308 would not have suggested immobilizing LF on a naturally occurring substrate via its N-terminus region. Therefore, European Patent Application '308 would not have made obvious either claim 38 or 39, so that this ground for rejection should be withdrawn.

XI. Kruzel *et al.* Do not Anticipate the Claimed Invention

US Patent 6,066,469 by Kruzel *et al.* ("Kruzel *et al.*") does not anticipate any of claims 1-3, 5, 18-20, 22, 31, 32, 102-104, 106, 115, 119, 124, 137, 138, 142-150, 154, 164, and 165 under 35 USC § 102(e). Kruzel *et al.* disclose the use of LF as a nutritional supplement, as an antiseptic to treat and prevent opportunistic bacterial, viral and fungal infections, and as a food-spoilage retardant. Kruzel *et al* neither broadly teach LF immobilized on a naturally occurring substrate via the N-terminus region of the LF, nor provide a specific

example of such an immobilized LF. (Barron Decl., ¶ 30.) The examiner asserts that:

"Kruzel *et al.* teach nutritional supplements comprising LF in combination with adjuvants or diluents such as cellulose, starch, tragacanth, and sodium carboxymethlycellulose . . . . Because the same components are present in the same defined dispersion, inherently the LF in the nutritional supplements of Kruzel *et al* will be immobilized via its N-terminus . . ."

A. Kruzel *et al.* does not Teach the Formation of Immobilized LF

Dr. Barron makes plain that Kruzel *et al.* does not disclose nor suggest any conditions under which the compounds could be mixed to result in the LF becoming attached via its N-terminus. (Barron Decl., ¶ 35.) He explains, "The mere presence in a mixture of LF and an adjuvant or a diluent, such as the solids cellulose, starch, tragacanth, and sodium carboxymethlycellulose would not inherently result in the LF becoming attached via its N-terminus." (Barron Decl., ¶ 33.)

B. Kruzel *et al* does not Disclose any Compounds having the Charge Required to Immobilize LF

Cellulose and starch do not carry any charges. (Barron Decl., ¶ 34.) As a result, neither cellulose nor starch contains a region which will immobilize LF's positively charged N-terminus region. (*Id.*)

Applicant's argument is fully supported by Dr. Barron's declaration. Applicant has never asserted that all naturally occurring "substrates" are useful. On the contrary, the substrates are subject to the limitation that the LF must be immobilized via its N-terminal region. Therefore, the claims do not read on compounds lacking the negatively charged region needed to immobilize

the N-terminus region of LF, such as cellulose or starch. Therefore, the rejection of claims 1-3, 5, 18-20, 22, 31, 32, 102-104, 106, 115, 119, 124, 137, 138, 142-150, 154, 164, and 165 as being anticipated by Kruzel *et al.* should be withdrawn.

(9) Conclusion

For the foregoing reasons, Claims 1, 2, 5, 11, 18-20, 22, 28, 31, 32, 38, 39, 86, 101-104, 106, 115-117, 119-124, 126-129, 131-138, 142-151, 153, 154, 157-159, 162-165, 171-173, 175, 176, 179-181, 184-187, 193-197, and 200-202, all of the claims on appeal, should be found allowable.

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Respectfully submitted,

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APPENDIX, CLAIMS

(From Applicant's Reply to January 7, 2005 Office Action)

1. A composition of matter comprising a dispersion of isolated lactoferrin immobilized on a naturally occurring substrate not including gelatin via the N-terminus region of the lactoferrin.

2. The composition in accordance with claim 1, wherein the naturally occurring substrate not including gelatin is a protein, a polysaccharide, a nucleic acid, or a nucleotide.

3. The composition in accordance with claim 1, wherein the naturally occurring substrate not including gelatin is collagen, fibronectin, casein, mucin, heparan-sulfate, carrageenan, deoxyribonucleic acid, or adenosine triphosphate.

4. The composition in accordance with claim 1, wherein the naturally occurring substrate not including gelatin is a galactose-rich polysaccharide comprising mainly galactose residues and derivatized galactose residues.

5. The composition of claim 1, wherein the dispersion is an aqueous solution, an aqueous emulsion, a colloid, a suspension, a powder, or a granular solid.

6. A composition of matter comprising a dispersion of isolated lactoferrin immobilized on a naturally occurring substrate via the N-terminus region of the lactoferrin, and native lactoferrin.

7. The composition in accordance with claim 6, wherein the concentration of immobilized lactoferrin and native lactoferrin in the dispersion is from about 0.05% wt/vol to about 2.5 % wt/vol.

8. The composition in accordance with claim 6, wherein the molar ratio of immobilized lactoferrin to native lactoferrin is a ratio of from about 1:1 to about 1:10.

9. The composition in accordance with claim 6, wherein the molar ratio of immobilized lactoferrin to native lactoferrin is a ratio of from about 1:1 to about 1:5.

10. The composition in accordance with claim 6, wherein the composition comprises about 1 % wt/vol immobilized lactoferrin and about 1 % wt/vol native lactoferrin.

11. The composition in accordance with claim 1, wherein the composition further comprises a buffer system.

12. The composition in accordance with claim 11, wherein the buffer system contains a physiologically acceptable acid, a physiologically acceptable base, and a physiologically acceptable salt.

13. The composition in accordance with claim 12, wherein the physiologically acceptable acid is oxalic acid, ethylenediamine tetraacetic acid, carbonic acid, or citric acid; the physiologically acceptable base is sodium bicarbonate, potassium bicarbonate, sodium carbonate, or potassium carbonate; and the physiologically acceptable salt is calcium chloride, potassium chloride or sodium chloride.

14. A composition of matter comprising an aqueous buffer solution containing a physiologically acceptable acid selected from the group consisting of oxalic acid, ethylenediamine tetraacetic acid, carbonic acid, and citric acid; a physiologically acceptable base; and a physiologically acceptable salt selected from the group consisting of calcium chloride, potassium chloride, and sodium chloride, wherein the ratio of acid to base to salt is 0.1 to 0.0001 M (acid) : 1 to 0.001 M (base) : 10 to 0.01M (salt) and containing a mixture of native lactoferrin and isolated lactoferrin immobilized on a galactose-rich polysaccharide comprising mainly galactose residues and derivatized galactose residues, collagen, fibronectin, casein, mucin, heparan-sulfate, carrageenan, deoxyribonucleic acid, or adenosine triphosphate via the N-terminus region of the lactoferrin, in a native lactoferrin to isolated immobilized lactoferrin molar ratio of from about 1:1 to about 1:5 and in a concentration of from about 0.001 to about 2.5 % wt/vol.

15. The composition in accordance with claim 14, wherein the lactoferrin is immobilized on a galactose-rich polysaccharide comprising mainly galactose residues and derivatized galactose residues.

16. The composition in accordance with claim 14, wherein the mixture comprises about 1 % wt/vol immobilized lactoferrin and about 1% wt/vol native lactoferrin.

17. The composition in accordance with claim 14, wherein the physiologically acceptable acid is citric acid, the physiologically acceptable base is sodium bicarbonate and the physiologically acceptable salt is sodium chloride.

18. A method for reducing the microbial contamination of a composition subject to microbial contamination by a microbe, comprising: treating the composition with a sufficient amount of isolated lactoferrin immobilized on a naturally occurring substrate not including gelatin via the N-terminus region of the lactoferrin to reduce microbial contamination.

19. The method in accordance with claim 18, wherein the naturally occurring substrate, not including gelatin, is a protein, a polysaccharide, a nucleic acid, or a nucleotide.

20. The method in accordance with claim 18, wherein the naturally occurring substrate not including, gelatin is collagen, fibronectin, casein, mucin, heparan-sulfate, carrageenan, deoxyribonucleic acid, or adenosine triphosphate.

21. The method in accordance with claim 18, wherein the naturally occurring substrate, not including gelatin, is a galactose-rich polysaccharide comprising mainly galactose residues and derivatized galactose residues.

22. The method of claim 18, wherein the composition is an aqueous solution, an aqueous emulsion, a colloid, a suspension, a powder, or a granular solid.

23. The method in accordance with claim 18, further comprising applying a composition containing a mixture of immobilized lactoferrin and native lactoferrin.

24. The method in accordance with claim 23, wherein the concentration of the mixture in the composition is from about 0.001 to about 2.5% wt/vol.

25. The method in accordance with claim 23, wherein the molar ratio of immobilized lactoferrin to native lactoferrin in the mixture is in a ratio of from about 1:1 to about 1:10.

26. The method in accordance with claim 23, wherein the molar ratio of immobilized lactoferrin to native lactoferrin in the mixture is in a ratio of from about 1:1 to about 1:5.

27. The method in accordance with claim 23, wherein the mixture comprises about 1 % wt/vol immobilized lactoferrin and about 1 % wt/vol native lactoferrin.

28. The method in accordance with claim 22, wherein the aqueous solution further comprises a buffer system.

29. The method in accordance with claim 28, wherein the buffer system contains a physiologically acceptable acid, a physiologically acceptable base, and a physiologically acceptable salt.

30. The method in accordance with claim 29, wherein the physiologically acceptable acid is oxalic acid, ethylenediamine tetraacetic acid, carbonic acid, or citric acid; the physiologically acceptable base is sodium bicarbonate, potassium bicarbonate, sodium carbonate, or potassium carbonate; and the physiologically acceptable salt is calcium chloride, potassium chloride or sodium chloride.

31. The method of claim 18, wherein the microbe is a bacterium, a fungus, a protozoan, or a virus.

32. The method in accordance with claim 18, wherein the microbe is enterotoxigenic *Escherichia coli,* enteropathogenic *Escherichia coli, Shigella dysenteriae, Shigella flexneri, Salmonella typhimurium, Salmonella typhi, Salmonella abony, Salmonella dublin, Salmonella enteritidis, Salmonella hartford, Salmonella kentucky, Salmonella panama, Salmonella pullorum, Salmonella rostock, Salmonella thompson, Salmonella virschow, Enterobacter aerogenes, Vibrio cholerae, Yersinia enterocolitica, Campylobacter jejuni, Aeromonas hydrophila, Staphylococcus aureus, Staphylococcus hyicus, Staphylococcus epidermidis, Staphylococcus hominis, Staphylococcus warneri, Staphylococcus xylosus, Staphylococcus chromogenes, Streptococcus pyogenes, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus sanguis, Pediococcus acne, Bacillus cereus, Bacillus anthracis, Bacillus subtilis,* a *Brucella* species, *Listeria monocytogenes, Bordetella pertussis, Pseudomonas aeruginosa, Legionella pneumophila, Francisella tularensis, Candida albicans, Brochothrix thermospacta, Bacillus pumilus, Enterococcus faecium, Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Deinococcus radiopugnans, Deinococcus radiodurans, Deinobacter grandis, Acinetobacter radioresistens,* or *Methylobacterium radiotolerans.*

33. The method in accordance with claim 18, wherein the microbe is a verotoxic *Escherichia coli.*

34. The method in accordance with claim 33, wherein the verotoxic *Escherichia coli* is the serotype 0157:H7.

35. The method of Claim 18, wherein the microbe is a *Clostridium* species.

36. The method of Claim 35, wherein the species is *Clostridium perfringens, Clostridiumdifficile, Clostridiumbotulinum,* or *Clostridium tetani.*

37. The method of Claim 18, wherein the microbe is a protozoan selected from the group consisting of *Entamoeba histolytica, Naegleria flowleri, Giardia lamblia, Leishmania spp., Trichomonas vaginalis, Trypanosoma spp., Plasmodium spp.,* and *Taxoplasma spp.*

38. The method in accordance with claim 18, wherein the concentration of lactoferrin on the surface of the composition subject to microbial contamination is from about 0.0001 to about 10 mg /sq.inch.

39. The method in accordance with claim 38, wherein the concentration of lactoferrin on the surface of the composition subject to microbial contamination is from about 0.01 to about 1 mg/sq. inch.

40. A method for inhibiting the microbial contamination of a composition subject to microbial contamination comprising treating the composition with an aqueous buffer solution containing a physiologically acceptable acid selected from the group consisting of oxalic acid, ethylenediamine tetraacetic acid, carbonic acid, and citric acid; a physiologically acceptable base; and a physiologically acceptable salt selected from the group consisting of calcium chloride, potassium chloride, and sodium chloride, wherein the ratio of acid to base to salt is 0.1 to 0.0001M (acid): 1 to 0.001 M (base): 10 to 0.01 M (salt) and containing a mixture of native lactoferrin and isolated lactoferrin immobilized on a galactose-rich

polysaccharide comprising mainly galactose residues and derivatized galactose residues, collagen, gelatin, fibronectin, casein, mucin, heparan-sulfate, carrageenan, deoxyribonucleic acid, or adenosine triphosphate via the N-terminus region of the lactoferrin, in a native lactoferrin to isolated immobilized lactoferrin molar ratio of from about 1:1 to about 1:5 and in a concentration of from about 0.001 to about 2.5 % wt/vol.

41. The method in accordance with claim 40, wherein the lactoferrin is immobilized on galactose-rich polysaccharide comprising mainly galactose residues and derivatized galactose residues.

42. The method in accordance with claim 40, wherein the mixture comprises about 1 % wt/vol immobilized lactoferrin and about 1 % wt/vol native lactoferrin.

43. The method in accordance with claim 40, wherein the physiologically acceptable acid is citric acid, the physiologically acceptable base is sodium bicarbonate and the physiologically acceptable salt is sodium chloride.

44. The method of claim 40, wherein the microbe is bacterium, a fungus, a protozoan, or a virus.

45. The method in accordance with claim 40, wherein the microbe is enterotoxigenic *Escherichia coli,* enteropathogenic *Escherichia coli, Shigella dysenteriae, Shigella flexneri, Salmonella typhimurium, Salmonella typhi, Salmonella abony, Salmonella dublin, Salmonella enteritidis, Salmonella hartford, Salmonella kentucky, Salmonella panama, Salmonella pullorum, Salmonella rostock, Salmonella thompson, Salmonella virschow, Enterobacter*

aerogenes, Vibrio cholerae, Yersinia enterocolitica, Campylobacter jejuni, Aeromonas hydrophila, Staphylococcus aureus, Staphylococcus hyicus, Staphylococcus epidermidis, Staphylococcus hominis, Staphylococcus warneri, Staphylococcus xylosus, Staphylococcus chromogenes, Streptococcus pyogenes, Streptococcus pneumoniae, Streptococcus mutans, Streptococccus sanguis, Pediococcus acne, Bacillus cereus, Bacillus anthracis, Bacillus subtilis, a *Brucella* species, *Listeria monocytogenes, Legionella pneumophila, Bordetella pertussis, Pseudomonas aeruginosa, Francisella tularensis, Candida albicans, Brochothrix thermospacta, Bacillus pumilus, Enterococcus faecium, Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Deinococcus radiopugnans, Deinococcus radiodurans, Deinobacter grandis, Acinetobacter radioresistens,* or *Methylobacterium radiotolerans.*

46. The method in accordance with claim 40, wherein the microbe is a verotoxic *Escherichia coli.*

47. The method in accordance with claim 46, wherein the verotoxic *Escherichia coli is* the serotype 0157:H7.

48. The method of Claim 40, wherein the microbe is a *Clostridium sp.*

49. The method of Claim 48, wherein the species is *Clostridium perfringens, Clostridium difficile, Clostridium botulinum,* or *Clostridium tetani.*

50. **CANCELLED**

51. The method in accordance with claim 40, wherein the ratio of acid to base to salt is 0.01 to 0.001 M (acid) : 0.1 to 0.01 M (base) : 1 to 0.1 M(salt).

52. **CANCELLED**

53. **CANCELLED**

54. **CANCELLED**

55. **CANCELLED**

56. The method in accordance with claim 18, wherein the composition subject to microbial contamination is a foodstuff.

57. The method in accordance with claim 56, wherein the foodstuff is a meat product.

58. The method of claim 57, wherein the meat product is a beef product, a pork product, or a poultry product.

59. The method in accordance with claim 40, wherein the composition subject to microbial contamination is a foodstuff.

60. The method in accordance with claim 59, wherein the composition is a meat product.

61. The method of Claim 60, wherein the meat product is a beef product, a pork product, or a poultry product.

62. The method of claim 57, wherein the meat product is veal, lamb, sheep, goat, elk, deer, antelope, horse, or dog.

63. The method of claim 60, wherein the meat product is veal, lamb, sheep, goat, elk, deer, antelope, horse, or dog.

64. The method of claim 56, wherein the foodstuff comprises a surface and/or flesh of a marine or freshwater aquatic organism.

65. The method of claim 64, wherein the aquatic organism is a fish, mollusk, or crustacean.

66. The method of claim 59, wherein the foodstuff comprises a surface and/or flesh of a marine or freshwater aquatic organism.

67. The method of claim 66, wherein the aquatic organism is a fish, mollusk, or crustacean.

68. The method of claim 56, wherein the foodstuff comprises a vegetable foodstuff.

69. The method of claim 59, wherein the composition comprises a vegetable foodstuff.

70. A method for reducing the microbial contamination of a meat product subject to microbial contamination by a microbe, comprising: applying to the meat product a composition containing a physiologically acceptable acid selected from the group consisting of oxalic acid, ethylenediamine tetraacetic acid, carbonic acid, and citric acid; a physiologically acceptable base; and a physiologically acceptable salt selected from the group consisting of calcium chloride, potassium chloride, and sodium chloride, wherein the molar ratio of acid to base to salt is 0.1 to 0.0001 (acid) : 1 to 0.001 (base) : 10 to 0.01 (salt)

and containing a mixture of native lactoferrin and isolated lactoferrin immobilized on a galactose-rich polysaccharide comprising mainly galactose residues and derivatized galactose residues, collagen, gelatin, fibronectin, casein, mucin, heparan-sulfate, carrageenan, deoxyribonucleic acid, or adenosine triphosphate via the N-terminus region of the lactoferrin, in a native lactoferrin to isolated immobilized lactoferrin molar ratio of from about 1:1 to about 1:5 and in a concentration of from about 0.001 to about 2.5 % wt/vol.

71. The method of claim 70, wherein the composition is an aqueous solution, an aqueous emulsion, a colloid, a suspension, a powder, or a granular solid.

72. The method in accordance with claim 70, wherein the lactoferrin is immobilized on a galactose-rich polysaccharide comprising mainly galactose residues and derivatized galactose residues.

73. The method in accordance with claim 70, wherein the mixture comprises about 1 % wt/vol immobilized lactoferrin and about 1 % wt/vol native lactoferrin.

74. The method in accordance with claim 70 wherein the physiologically acceptable acid is citric acid, the physiologically acceptable base is sodium bicarbonate and the physiologically acceptable salt is sodium chloride.

75. The method of claim 70, wherein the microbe is a bacterium, a fungus, a protozoan, or a virus.

76. The method in accordance with claim 70, wherein the microbe is enterotoxigenic *Escherichia coli,* enteropathogenic *Escherichia coli, Shigella dysenteriae, Shigella flexneri, Salmonella typhimurium, Salmonella typhi, Salmonella abony, Salmonella dublin, Salmonella enteritidis, Salmonella hartford, Salmonella kentucky, Salmonella panama, Salmonella pullorum, Salmonella rostock, Salmonella thompson, Salmonella virschow, Enterobacter aerogenes, Vibrio cholerae, Yersinia enterocolitica, Campylobacter jejuni, Aeromonas hydrophila, Staphylococcus aureus, Staphylococcus hyicus, Staphylococcus epidermidis, Staphylococcus hominis, Staphylococcus warneri, Staphylococcus xylosus, Staphylococcus chromogenes, Streptococcus pyogenes, Streptococcus pneumoniae, Streptococcus mutans, Streptococccus sanguis, Pediococcus acne, Bacillus cereus, Bacillus anthracis, Bacillus subtilis,* a *Brucella* species, *Listeria monocytogenes, Legionella pneumophila, Bordetella pertussis, Pseudomonas aeruginosa, Francisella tularensis, Candida albicans, Brochothrix thermospacta, Bacillus pumilus, Enterococcus faecium, Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Deinococcus radiopugnans, Deinococcus radiodurans, Deinobacter grandis, Acinetobacter radioresistens,* or *Methylobacterium radiotolerans.*

77. The method in accordance with claim 70, wherein the microbe is a verotoxic *Escherichia coli.*

78. The method in accordance with claim 77, wherein the verotoxic *Escherichia coli* is the serotype 0157: H7.

79. The method of claim 70, wherein the microbe is a *Clostridium* species.

80. The method of claim 79, wherein the species is *Clostridium perfringens, Clostridium difficile, Clostridium botulinum,* or *Clostridium tetani.*

81. The method in accordance with claim 70 wherein the concentration of lactoferrin on the surface of the meat product is from about 0.0001 to about 10 mg /sq. inch.

82. The method in accordance with claim 70, wherein the concentration of lactoferrin on the surface of the meat product is from about 0.01 to about 1 mg/sq. inch.

83. The method in accordance with claim 70, wherein the meat product is a beef product, a pork product, or a poultry product.

84. The method of claim 70, wherein the meat product is veal, lamb, sheep, goat, elk, deer, antelope, horse, or dog.

85. A foodstuff containing: isolated lactoferrin immobilized on a naturally occurring substrate via the N-terminus region of the lactoferrin in a concentration between about 0.0001 and about 10 mg per gram of the foodstuff.

86. The foodstuff in accordance with claim 85, wherein the composition is a meat product.

87. The foodstuff of Claim 86, wherein the meat product is a beef product, a pork product, or a poultry product.

88. The foodstuff of claim 86, wherein the meat product is veal, lamb, sheep, goat, elk, deer, antelope, horse, or dog.

89. The foodstuff of claim 86, wherein the foodstuff comprises a surface and/or flesh of a marine or freshwater aquatic organism.

90. The foodstuff of claim 89, wherein the aquatic organism is a fish, mollusk, or crustacean.

91. The foodstuff of claim 85, wherein the foodstuff comprises a vegetable foodstuff.

92. The foodstuff of claim 86, wherein said foodstuff is a packaged foodstuff.

93. A method of inhibiting the growth and/or adhesion of a microbial species on a foodstuff, comprising: treating a food-contacting surface of a material for food packaging or food handling with an isolated lactoferrin immobilized on a naturally occurring substrate via the N-terminus region of the lactoferrin; and contacting a foodstuff with said surface, whereby the growth and/or adhesion of a microbial species on said foodstuff is inhibited.

94. The method of Claim 93, wherein said food packaging or handling material is a cellulosic polymer.

95. The method of Claim 93, wherein said food packaging or handling material is paper, wood, or cardboard.

96. The method of Claim 93, wherein said food-contacting surface comprises a surface belonging to a shear wrap, a cellophane, a wrapping paper, a waxed paper, a bag, a carton, a box, a tray, a plate, a bowl, a food storage vessel, a serving dish, a cup, a bin, a jar, or a bottle.

97. The method of Claim 97, wherein said food-contacting surface comprises a surface belonging to a glove, a mitt, a fork, a spoon, a knife, a slicer, a tong, a ladle, a scoop, a cup, a processor, a juicer, a grinder, a press, a hook, a chipper, a peeler, a cutter, a screw, an opener, a chute, a spatula, a cutting board, a kneading board, a rack, or a shelf.

98. A food container or food-handling implement, said container or implement having a food-contacting surface, said surface treated with an isolated lactoferrin immobilized on a naturally occurring substrate via the N-terminus region of the lactoferrin in an amount effective to inhibit the growth and/or adhesion of a microbial species on said surface.

99. The food container or food-handling implement of Claim 98, wherein said container or implement is a shear wrap, a cellophane, a wrapping paper, a waxed paper, a bag, a carton, a box, a tray, a plate, a bowl, a food storage vessel, a serving dish, a cup, a bin, a jar, a bottle, a glove, a mitt, a fork, a spoon, a knife, a slicer, a tong, a ladle, a scoop, a processor, a juicer, a grinder, a press, a hook, a chipper, a screw, a cutter, a peeler, an opener, a chute, a spatula, a cutting board, a kneading board, a rack, or a shelf.

100. The food container or food-handling implement of Claim 98, having an amount of between about 0.0001 to about 10 mg /square inch of said food-contacting surface.

101. An antimicrobial cleanser, polish, paint, spray, soap, or detergent for applying to an inanimate surface, containing an isolated lactoferrin immobilized on a naturally occurring substrate not including gelatin via the N-terminus region of the lactoferrin in an amount effective to inhibit the growth and/or adhesion of a microbial species on said surface.

102. A composition of matter comprising a dispersion of isolated lactoferrin immobilized on a naturally occurring substrate not including gelatin via the N-terminus region of the lactoferrin; and at least one pharmaceutically acceptable carrier.

103. The composition in accordance with claim 102, wherein the naturally occurring substrate, not including gelatin, is a protein, a polysaccharide, cellulose, a nucleic acid, or a nucleotide.

104. The composition in accordance with claim 102, wherein the naturally occurring substrate not including, gelatin is collagen, fibronectin, casein, mucin, heparin-sulfate, carrageenan, deoxyribonucleic acid, or adenosine triphosphate.

105. The composition in accordance with claim 102, wherein the naturally occurring substrate is a galactose-rich polysaccharide comprising mainly galactose residues and derivatized galactose residues.

106. The composition of claim 105, wherein the dispersion is an aqueous solution, an aqueous emulsion, a colloid, a suspension, a powder, or a granular solid.

107. The composition in accordance with claim 102, further comprising native lactoferrin.

108. The composition in accordance with claim 107, wherein the concentration of immobilized lactoferrin and native lactoferrin in the dispersion is from about 0.05% wt/vol to about 2.5 % wt/vol.

109. The composition in accordance with claim 107, wherein the molar ratio of immobilized lactoferrin to native lactoferrin is a ratio of from about 1:1 to about 1:10.

110. The composition in accordance with claim 107, wherein the molar ratio of immobilized lactoferrin to native lactoferrin is a ratio of from about 1:1 to about 1:5.

111. The composition in accordance with claim 107, wherein the composition comprises about 1 % wt/vol immobilized lactoferrin and about 1 % wt/vol native lactoferrin.

112. The composition in accordance with claim 107, wherein the composition further comprises a buffer system.

113. The composition in accordance with claim 112, wherein the buffer system contains a physiologically acceptable acid, a physiologically acceptable base, and a physiologically acceptable salt.

114. The composition in accordance with claim 113, wherein the physiologically acceptable acid is oxalic acid, ethylenediamine tetraacetic acid, carbonic acid, or citric acid; the physiologically acceptable base is sodium

bicarbonate, potassium bicarbonate, sodium carbonate, or potassium carbonate; and the physiologically acceptable salt is calcium chloride, potassium chloride or sodium chloride.

115. The composition of claim 102, wherein the carrier is selected from the group consisting of solid, semisolid or liquid glucose, lactose, sucrose, gum acacia, agar, petrolatum, lanolin, dimethyl sulfoxide, normal saline, phosphate buffered saline, sodium alginate, bentonite, carbomer, carboxymethylcellulose, carageenan, powdered cellulose, cholesterol, gelatin, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, octoxynol 9, oleyl alcohol, polyvinyl alcohol, povidone, propylene glycol monostearate, sodium lauryl sulfate, sorbitan esters, stearyl alcohol, tragacanth, xanthan gum, chondrus, glyercin, trolamine, avocado oil, almond oil, coconut oil, coconut butter, propylene glycol, ethyl alcohol, malt, and malt extract.

116. The composition of claim 102, further comprising a pharmaceutically acceptable emulsifier.

117. The composition of claim 116, wherein the emulsifier is selected from the group consisting of monoglyceride compounds, diglyceride compounds, glycerol, phosphatidyl ethanolamine, phosphatidyl choline, or lecithin.

118. The composition in accordance with claim 14, wherein the molar ratio of acid to base to salt is 0.01 to 0.001 M (acid): 0.1 to 0.01 M (base) : 1 to 0.1 M(salt).

119. The composition of claim 102, wherein the composition is formulated in a cosmetic, a cleanser, a food supplement, or a medicament.

120. The composition of claim 102, wherein the cosmetic, cleanser, food supplement, or medicament is formulated for applying to an external surface of a vertebrate subject.

121. The composition of claim 120, wherein the vertebrate subject is a human.

122. The composition of claim 120, wherein the vertebrate subject is a non-human vertebrate.

123. The composition of claim 119, wherein the cleanser is formulated as a pharmaceutically acceptable skin cleanser.

124. The composition of claim 119, wherein the medicament is formulated in a pharmaceutically acceptable delivery system.

125. The composition of claim 124, wherein said delivery system is an injection, intravenous drip, inhalant, or implant delivery system.

126. The composition of claim 124, wherein said delivery system is a transdermal delivery system.

127. The composition of claim 124, wherein said delivery system is a transmucosal delivery system.

128. The composition of claim 124, wherein said delivery system is an oral transmucosal delivery system.

129. The composition of claim 124, wherein said delivery system is a vaginal transmucosal delivery system.

130. The composition of claim 124, wherein said delivery system comprises an adhesive patch.

131. The composition of claim 124, wherein said delivery system comprises a gel, cream, ointment, suppository, sanitary wipe, bandage, or shampoo.

132. The composition of claim 124, wherein the delivery system is a mouth wash, gargle solution, denture cleanser, or dentifrice.

133. The composition of claim 124, wherein the delivery system is a toothpaste or chewing gum.

134. The composition of claim 124, wherein the medicament is formulated in a urogenital, rectal, or colonic delivery system.

135. The composition of claim 119, wherein the composition further comprises an antibiotic or probiotic agent.

136. The composition of claim 124, wherein the delivery system is a suppository, gel, or foam.

137. The composition of claim 127, wherein the medicament is formulated in an ingestive delivery system.

138. The composition of claim 137, wherein the ingestive delivery system is a tablet, capsule, caplet, troche, lozenge, coated or uncoated microspheres or particles, dispersible powder or granules, syrup, elixir, beverage, or food additive.

139. The composition of claim 138, wherein the tablet or capsule comprises a controlled release coating.

140. The composition of claim 138, wherein the ingestive delivery system comprises an enteric coating to prevent esophageal or gastric release of immobilized lactoferrin.

141. The composition of claim 124, wherein the delivery system comprises a lavage or enema.

142. The composition of claim 119, wherein the medicament is formulated for treating a human.

143. The composition of claim 142, wherein the composition is formulated for pediatric use.

144. The composition of claim 119, wherein the medicament is formulated for veterinary use.

145. The composition of claim 114, wherein the composition is formulated for use in a domestic or farm animal.

146. The composition of claim 114, wherein the composition is formulated for use in a non-human mammal or bird.

147. The composition of claim 146, wherein the composition is formulated for use in a non-human primate, mouse, rat, rabbit, gerbil, hamster, canine, feline, ovine, bovine, swine, pachyderm, equine, or marine mammal.

148. The composition of claim 146, wherein the composition is formulated for use in a chicken, duck, goose, turkey, ostrich, emu, dove, pigeon, quail, pheasant, peafowl, or guinea fowl.

149. The method of claim 18, wherein said composition subject to microbial contamination is a human.

150. The method of claim 149, wherein treating includes administering to said human said composition by a pharmaceutically acceptable delivery route.

151. The method of claim 150, wherein said delivery route is non-systemic.

152. The method of claim 151, wherein said non-systemic delivery route is a urogenital, rectal, or colonic delivery route.

153. The method of claim 151, wherein said non-systemic delivery route is a topical application of a cream, gel, or ointment.

154. The method of claim 150, wherein said delivery route is systemic.

155. The method of claim 154 wherein said systemic delivery route is by ingestion, injection, intravenous drip, inhalant, or implant.

156. The method of claim 154 wherein said systemic delivery route is a transdermal delivery route.

157. The method of claim 154 wherein said systemic delivery route is a transmucosal delivery route.

158. The method of claim 154, wherein the microbial contamination of a human to be reduced is in the gastrointestinal system of the human.

159. The method of claim 150, wherein treating further comprises administering an antimicrobial agent or probiotic agent in conjunction with the immobilized lactoferrin.

160. The method of claim 159, wherein the probiotic agent is a species of *Bifidobacterium, Streptococcus, Pediococcus, Lactococcus,* or *Lactobacillus.*

161. The method of claim 160, wherein the probiotic agent is *Bifidobacterium bifidum, Bifidobacterium longum, Bifidobacterium animalis, Streptococcus lactis, Streptococcus cremoris, Streptococcus thermophilus, Pediococcus pentoseus, Lactococcus lactis, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus plantarum, Lactobacillus reuteri, Lactobacillus bulgaricus, Lactobacillus paracasei,* or *Lactobacillus casei.*

162. The method of claim 159, wherein the antimicrobial agent is an antibiotic.

163. The method of claim 162, wherein the antimicrobial agent is neomycin, metronidazole, teicoplanin, vancomycin, ciprofloxacin, doxycycline, tetracycline, augmentin, erythromycin, chloramphenicol, cephalexin, penicillin, ampicillin, kanamycin, rifamycin, rifaximin, rifampin, clindamycin, trimethoprim, a 4-amino salicylate compound, a 5-aminosalicylate compound, a sulfonamide compound, a betalactam compound, an aminoglycoside compound, a macrolide compound, or a quinolone compound.

164. The method of claim 149, wherein the microbe is bacterium, a fungus, a protozoan, or a virus.

165. The method in accordance with claim 149, wherein the microbe is enterotoxigenic *Escherichia coli,* enteropathogenic *Escherichia coli, Shigella dysenteriae, Shigella flexneri, Salmonella typhimurium, Salmonella typhi, Salmonella abony, Salmonella dublin, Salmonella enteritidis, Salmonella hartford, Salmonella kentucky, Salmonella panama, Salmonella pullorum, Salmonella rostock, Salmonella thompson, Salmonella virschow, Enterobacter aerogenes, Vibrio cholerae, Yersinia enterocolitica, Campylobacter jejuni, Aeromonas hydrophila, Staphylococcus aureus, Staphylococcus hyicus, Staphylococcus epidermidis, Staphylococcus hominis, Staphylococcus warneri, Staphylococcus xylosus, Staphylococcus chromogenes, Streptococcus pyogenes, Streptococcus pneumoniae, Streptococcus mutans, Streptococccus sanguis, Pediococcus acne, Bacillus cereus, Bacillus anthracis, Bacillus subtilis, a Brucella species, Listeria monocytogenes, Legionella pneumophila, Bordetella pertussis, Pseudomonas aeruginosa, Francisella tularensis, Candida albicans, Brochothrix thermospacta, Bacillus pumilus, Enterococcus faecium,*

Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Deinococcus radiopugnans, Deinococcus radiodurans, Deinobacter grandis, Acinetobacter radioresistens, or *Methylobacterium radiotolerans.*

166. The method in accordance with claim 149, wherein the microbe is a verotoxic *Escherichia coli.*

167. The method in accordance with claim 166, wherein the verotoxic *Escherichia coli* is the serotype 0157:H7.

168. The method of claim 149, wherein the microbe is a *Clostridium* species.

169. The method of claim 168, wherein the species is *Clostridium perfringens, Clostridium difficile, Clostridium botulinum, or Clostridium tetani.*

170. The method of claim 149, wherein the microbe is a protozoan selected from the group consisting of *Entamoeba histolytica, Naegleria flowleri, Giardia lamblia, Leishmania spp., Trichomonas vaginalis, Trypanosoma spp., Plasmodium spp.*, or *Taxoplasma spp.*

171. The method of claim 18, wherein said composition subject to microbial contamination is a non-human vertebrate.

172. The method of claim 171, wherein treating includes administering to said non-human vertebrate said composition by a pharmaceutically acceptable delivery route.

173. The method of claim 172, wherein said delivery route is non-systemic.

174. The method of claim 173, wherein said nonsystemic delivery route is a urogenital, rectal, or colonic delivery route.

175. The method of claim 173, wherein said nonsystemic delivery route is a topical application of a cream, gel, or ointment.

176. The method of claim 172, wherein said delivery route is systemic.

177. The method of claim 176, wherein said systemic delivery route is by ingestion, injection, intravenous drip, inhalant, or implant.

178. The method of claim 176, wherein said systemic delivery route is a transdermal delivery route.

179. The method of claim 176, wherein said systemic delivery route is a transmucosal delivery route.

180. The method of claim 171, wherein the microbial contamination of a non-human vertebrate to be reduced is in the gastrointestinal system of the non-human vertebrate.

181. The method of claim 172, wherein treating further comprises administering an antimicrobial agent or probiotic agent in conjunction with the immobilized lactoferrin.

182. The method of claim 181, wherein the probiotic agent is a species of *Bifidobacterium, Streptococcus, Pediococcus, Lactococcus, or Lactobacillus.*

183. The method of claim 182, wherein the species is *Bifidobacterium bifidum, Bifidobacterium longum, Bifidobacterium animalis, Streptococcus lactis, Streptococcus cremoris, Streptococcus thermophilus, Pediococcus pentoseus, Lactococcus lactis, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus plantarum, Lactobacillus reuteri, Lactobacillus bulgaricus, Lactobacillus paracasei,* or *Lactobacillus case.*

184. The method of claim 181, wherein the antimicrobial agent is an antibiotic.

185. The method of claim 184, wherein the antimicrobial agent is neomycin, metronidazole, teicoplanin, vancomycin, ciprofloxacin, doxycycline, tetracycline, augmentin, erythromycin, chloramphenicol, cephalexin, penicillin, ampicillin, kanamycin, rifamycin, rifaximin, rifampin, clindamycin, trimethoprim, a 4-amino salicylate compound, a 5-aminosalicylate compound, a sulfonamide compound, a betalactam compound, an aminoglycoside compound, a macrolide compound, or a quinolone compound.

186. The method of claim 171, wherein the microbe is a bacterium, a fungus, a protozoan, or a virus.

187. The method in accordance with claim 171, wherein the microbe is enterotoxigenic *Escherichia coli,* enteropathogenic *Escherichia coli, Shigella dysenteriae, Shigella flexneri, Salmonella typhimurium, Salmonella typhi, Salmonella abony, Salmonella dublin, Salmonella enteritidis, Salmonella hartford, Salmonella kentucky, Salmonella panama, Salmonella pullorum,*

Salmonella rostock, Salmonella thompson, Salmonella virschow, Enterobacter aerogenes, Vibrio cholerae, Yersinia enterocolitica, Campylobacter jejuni, Aeromonas hydrophila, Staphylococcus aureus, Staphylococcus hyicus, Staphylococcus epidermidis, Staphylococcus hominis, Staphylococcus warneri, Staphylococcus xylosus, Staphylococcus chromogenes, Streptococcus pyogenes, Streptococcus pneumoniae, Streptococcus mutans, Streptococccus sanguis, Pediococcus acne, Bacillus cereus, Bacillus anthracis, Bacillus subtilis, a *Brucella* species, *Listeria monocytogenes, Bordetella pertussis, Pseudomonas aeruginosa, Legionella pneumophila, Francisella tularensis, Candida albicans, Brochothrix thermospacta, Bacillus pumilus, Enterococcus faecium, Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Deinococcus radiopugnans, Deinoeoccus radiodurans, Deinobacter grandis, Aeinetobacter radio resistens, or Methylobacterium radiotolerans.*

188. The method in accordance with claim 171, wherein the microbe is a verotoxic *Escherichia coli.*

189. The method in accordance with claim 188, wherein the verotoxic *Escherichia coli* is the serotype 0157:H7.

190. The method of claim 171, wherein the microbe is a *Clostridium* species.

191. The method of claim 190, wherein the species is *Clostridium perfringens, Clostridium difficile, Clostridium botulinum, or Clostridium tetani.*

192. The method of claim 171, wherein the microbe is a protozoan selected from the group consisting of *Entamoeba histolytica, Naegleria flowleri,*

Giardia lamblia, Leishmania spp., Trichomonas vaginalis, Trypanosoma spp., Plasmodium spp., or *Taxoplasma spp.*

193. The method of claim 171, wherein said non-human vertebrate is a domestic or farm animal.

194. The method of claim 171, wherein said non-human vertebrate is a mammal or bird.

195. The method of claim 171, wherein said non-human vertebrate is a non-human primate, mouse, rat, rabbit, gerbil, hamster, canine, feline, ovine, bovine, swine, pachyderm, equine, or marine mammal.

196. The method of claim 171, wherein said non-human vertebrate is a chicken, duck, goose, turkey, ostrich, emu, dove, pigeon, quail, pheasant, peafowl, or guinea fowl.

197. The method of claim 18, wherein said composition subject to microbial contamination is a biological surface or a biological fluid.

198. The method of claim 197, wherein the fluid is a culture medium.

199. The method of claim 197, wherein the biological surface or fluid is in vitro.

200. The method of claim 197, wherein the biological surface is a cell surface, membrane surface, mucosal surface, epithelial surface, lumenal surface, skin surface, or eggshell surface.

201. The method of claim 197, wherein the biological surface is an epithelial or mucosal surface.

202. The method of claim 197, wherein the biological fluid is semen, blood, lymph, urine, prostatic fluid, saliva, gastric juice, mucus, synovial fluid, pleural exudate, peritoneal exudate, pericaridal exudate, or cerebro-spinal fluid.

203. **CANCELED**.